Public health implications of bovine somatotrophin use in dairying: discussion paper

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Introduction

The galactopoietic potency of bovine somatotrophin (bST; also known as growth hormone, bGH) has been known for over 50 years, but it is only since the 1980s that production of bST by recombinant DNA techniques has raised the prospect of its large scale use in dairying. Subcutaneous or intramuscular injections of approximately 30 mg/day can increase milk yields of dairy cows by over 20%. For use in commercial practice, it is generally proposed to administer 500-600 mg every 2 weeks. The four multinational companies producing bST have applied for product licences which would allow its sale to farmers but, to date, neither in Europe nor in the United States of America has authorization been granted.

Official pronouncements rejecting applications for product licences for bST have cited queries over animal welfare, but they have also specifically dismissed any hazards to consumers resulting from consumption of milk and dairy products. Indeed, for several years, milk from cows treated with bST for trial purposes has been allowed to enter the commercial food chain. Despite these assurances, a number of informed critics have voiced concern over possible effects of bST on public health. The purpose of this paper is to subject to rigorous examination assertions as to the safety of bST use in dairying. The two categories of risk to public health from use of bST, to be discussed below, are (i) the health of consumers of milk and dairy products, and (ii) public health consequences of changes in consumption of milk and dairy products following licensing of bST. Other perceived risks, such as those associated with the production process, are discussed elsewhere[1].

Health of consumers of milk and dairy products

Four types of compositional change in milk have been claimed to pose a threat to human safety.

Concentrations of nutrients

Reports of bST-induced changes in concentrations of fat and protein in milk show much variation. The nutritional status of the treated cow is an important determinant of the extent of the changes; and, particularly when cows are in negative energy balance (in early lactation or later in lactation when feed intake does not match energy needs), milk fat concentrations increase and those of protein decline[2].

In addition to changes in the total concentrations of fat and proteins, their compositions may also change. Thus, there are reports of increases of up to 27% in the concentration of long chain fatty acids[3], and of significant reductions in casein and increases in non-protein nitrogen concentrations, respectively[4]. There are few data on other milk nutrients: most suggest that only slight changes are induced by bST[5].

As milk does not have a constant composition, the changes induced might lie within the normal variation. Nevertheless, *mean* values seem likely to change in directions detrimental to the nutritional quality of milk. Health risks to individual consumers (eg in terms of milk fat composition) would thus depend on how much of the milk consumed was from cows treated with bST, and on factors such as the cows' nutritional status.

Concentration of bST

Most reports indicate that the concentration of bST in milk of treated cows is not significantly increased[6]. However, this does not mean that consumers are not exposed to the recombinant hormone, because the assay techniques employed cannot distinguish between the cow's natural bST and that injected. Since injection increases blood concentrations of bST substantially[5], virtually all the hormone in milk is likely to be of the recombinant type.

Because bovine and human somatotrophins differ substantially in amino acid sequence, bST is considered unlikely to be bioactive in humans[6]. Yet the possibility of bST bioactivity cannot be ruled out, as there are no reports of studies in which bST has been administered to healthy human volunteers. However, it is anticipated that, like other proteins, bST would undergo extensive proteolysis in the gut, and risks would be further reduced by pasteurization, which destroys 90% of bST in milk[6].

Concentration of insulin-like growth factor-1 (IGF-1)

IGF-1 is a normal constituent of both cows' and human milk, but following bST treatment its concentration increases. IGF-1 has a wide range of actions in the body. For example, it regulates transport processes (ion fluxes, glucose and amino acid uptake by cells); macromolecular synthesis (of RNA, DNA, proteins and lipids); and cell division and differentiation[7]. Given these properties, it is clearly important to establish whether the risks to consumers of increasing its concentration in milk are so low as to be considered negligible.

The first full report[8], in a refereed journal, on milk concentrations of IGF-1 in cows treated with bST, by Prosser *et al.* (1989), showed a 3.6 fold increase in IGF-1 concentration over a 7-day period of treatment, with the concentration increasing at the time when bST injections were stopped.

The potential significance of increased milk concentrations of IGF-1 for human safety is emphasized by the following facts:

(i) bovine IGF-1 has an identical amino acid sequence to human IGF-1[9];
(ii) IGF-1 in milk is not destroyed by pasteurization[10];
(iii) the normal presence of IGF-1 in both cows' and human milk, and its particularly high concentrations in the colostrum of both species[10,11], suggest that it performs a physiological function immediately post partum, promoting development of the neonatal gut[12].

For these reasons, concern has been expressed over risks to consumers from ingested IGF-1. For example, in the opinion of the Council on Scientific Affairs of the American Medical Association (1991)[13]: 'Further studies will be required to determine whether the ingestion of higher than normal concentrations of bovine insulinlike growth factor is safe for children, adolescents and adults'.

A number of other issues emphasize the need for more extensive investigation. Firstly, there is uncertainty about the accuracy of determinations of IGF-1 which employ (as in the study of Prosser *et al.*[8]) an acid-ethanol extraction procedure. For example, Mesiano *et al.*[14] claimed that significant amounts of binding protein survive the acid-ethanol extraction procedure, thus giving falsely low values for IGF-1.

Secondly, little is known of the effect of bST on the extent of IGF-1-binding in milk, which may have a significant effect on its biological activity. Recently, it has been reported[15] that in bovine colostrum at 2 days post partum, 82% of IGF-1 was in the free (unbound) state, but by day 4 this had decreased to 15%. Interestingly, Prosser *et al.*[8] reported that 'a significant proportion of IGF-1 in milk of cows treated with rbGH is unbound'. The physiological significance of IGF-1 binding is uncertain, since while it is generally believed that binding proteins inhibit its bioactivity, some proteins are believed to potentiate it[7].

Thirdly, no reports appear to have been published on the concentration in milk of a truncated form of IGF-1 (-3N:IGF-1), isolated from bovine colostrum by Francis *et al.*[16]. This peptide, which differs from IGF-1 by lacking the N-terminal tripeptide, Gly-Pro-Glu, has several important features. Its potency in stimulating DNA and protein syntheis in L6 rat myoblasts is up to 10 times greater than that of normal IGF-1, but it is underestimated by a factor of four using the standard IGF-1 assay technique. It accounted for about one-third of the total IGF-1 extracted from bovine colostrum.

The presence in colostrum of -3N:IGF-1 and of large amounts of free IGF-1 may be pointers to likely changes occurring in milk in response to bST treatment, since a strong parallel has been suggested between the increased milk secretion which occurs post partum and that following bST treatment[17].

The impracticability of conducting experiments on humans and the unfeasibility of acquiring epidemiological evidence, necessitate resort to experiments on laboratory animals to assess IGF-1 toxicity. In 1990, Juskevich and Guyer, of the US FDA, published results from which they concluded that 'bovine IGF-1 lacks oral activity in rats'[6]. The claimed evidence for this statement was provided by results of measurements of organ weights (heart, spleen, kidney and liver) and bone dimensions (epiphyseal width and tibial length) in groups of rats fed IGF-1 by gavage at four dose levels viz. 0, 0.02, 0.2 and 2.0 mg/kg per day. In the high dose group, several changes were significant, but even at the low dose (0.02 mg/kg) two statistically significant changes were reported in male rats, viz. an increase in tibia length ($P < 0.01$) and an increase in the relative heart weight (significance not stated). But because changes did not occur at the medium dose, the authors concluded 'these findings in the oral groups are considered contradictory in terms of effects of IGFs on growth indices and are therefore considered to be sporadic results'.

According to the principle advanced by K R Popper, 'The method of science is the method of bold conjectures and ingenious and severe attempts to refute them'[18]. This prescription rejects 'special pleading' as unscientific. But while the conjecture 'bovine IGF-1 lacks oral activity in rats' is unequivocally bold, the interpretation which is provided of the test results can hardly be said to demonstrate impressive severity and ingenuity. Thus, Juskevich and Guyer's dismissal of statistically significant results as unrelated to treatment, a practice which they adopt on two other occasions in the paper, is of questionable validity; and one that might be imprudent when an issue of such widespread public concern is at stake. Two options would seem to be reasonable: to require that the study be repeated or to take the statistics at face value.

If then it is assumed that oral IGF-1 at 0.02 mg/kg per day is biologically active in rats, how does this relate to the dose of IGF-1 to which a human consumer of milk would be subjected? Hammond *et al.*[19], of the Monsanto Agricultural Company, have provided a model for the appropriate calculation by referring to a milk intake of one litre per day by a 10 kg infant. Estimates of the IGF-1 content of milk in bST treated animals vary widely, but if data of Schams[20] are used (because they are among the highest values quoted), then such milk contains up to 25 μg/l IGF-1, ie the 10 kg infant is exposed to 2.5 μg/kg. This is one eighth of the dose shown to give statistically significant effects in rats. However, in view of the uncertainty attached to extrapolating from results obtained in rats, a safety margin needs to be built into the calculation. EEC directive 81/852 defines the criterion of acceptability 'to be a dose devoid of effect in man . . . or a safety margin of 1/100'[21]. According to this criterion, the infant would be exposed to a dose of IGF-1 which was 12.5 times the recommended minimum.

Even these calculations may underestimate the risk because, firstly, no dose of IGF-1 lower than 0.02 mg/kg was used in the rat experiments and, secondly, the safety factor of one hundred is known to have been totally inadequate in many previous toxicity studies. In, perhaps, the most notorious case in recent history, that of the drug thalidomide, a safety factor of 4000 was too small.

The claim that such levels of IGF-1 in milk are safe depends on the fact that some estimates of IGF-1 in milk of untreated cows[6] are as high as those in treated animals, so that if the growth factor is biologically active, milk drinkers might always have been exposed to significant bioactivity. However, large scale adoption of bST treatment would inevitably increase the mean concentration of IGF-1 in milk, by a factor of approximately two according to many published data, and cause some concentrations to

exceed the upper limit of the normal range. But more importantly, the *nature* of the extra IGF-1 in milk, ie whether it is in the free and/or more bioactive truncated form, is unknown.

Moreover, the claim that concentrations of IGF-1 in milk of bST-treated cows are in the physiological range, while scientifically accurate, can be misleading. Thus, one study showed that the IGF-1 concentration in colostrum declined from more than 150 μg/l at calving to 25 μg/l within 4 days[22]. But this is not of significance for consumers, because colostrum is not marketed.

The discussion above has focused on possible systemic effects of IGF-1. However, this is not the only way in which IGF-1 might act, because it stimulates proliferation of intestinal epithelial cells in vitro, at concentrations equivalent to those occurring in bovine mature milk[23]. That this is an issue of significant medical concern is illustrated by the following statement in the report of a US National Institutes of Health Expert Committee: 'Whether the additional amount of insulin-like growth factor 1 in milk from [bST-treated] cows has a local effect on the esophagus, stomach or intestines is unknown'[24]. Among the report's six recommendations was 'Determine the acute and chronic actions of IGF-1, if any, in the upper gastrointestinal tract'.

In summary, it would be imprudent to assume that the increased concentration of IGF-1 in milk of bST-treated cows presents no risks to human health until more information has been obtained on a number of issues. These include: (i) accurate determinations of the effect of bST on concentrations of total IGF-1 in milk; (ii) the effect of bST on the percentage of IGF-1 in the free form in milk, and its physiological significance; (iii) the effect of bST on the concentration of -3N:IGF-1 in milk; (iv) the local action of IGF-1 on tissues of the upper gastrointestinal tract of consumers; (v) the degree to which IGF-1 is absorbed across the gut wall in consumers.

Presence in milk of antibiotics and antibiotic-resistant bacteria

High yielding cows are prone to metabolic stress, which becomes evident in high rates of infectious disease, immune system dysfunction and reproductive problems[25]. Since bST treatment moves cows into the higher-yielding category, it would be anticipated that disease incidence would increase with bST treatment, irrespective of whether hormonal treatment *per se* induces disease. However, another important aspect of the response to bST is the strong parallel which it shows, physiologically and biochemically, with the increased milk secretion rate which occurs at lactogenesis[17]. This is particularly important because cows yielding the same amount of milk are, in general, two to three times more susceptible to disease in the ascending than in the descending phase of lactation[25].

The decreased welfare of cows receiving bST over two lactation periods is graphically illustrated by a recent report from a Monsanto Company laboratory[26]. The incidences of digestive disorders, lameness and clinical mastitis were increased in treated cows, the most severe disorders being associated with higher doses of bST. It is a telling fact that of the 62 cows treated with bST, eight died or became moribund (four mastitis cases, two pneumonia cases; one case of abomasal displacement; and one case of Johne's disease), whereas this applied to none of the 20 control cows. Three of these eight cases received bST at the prospective commercial dose.

The treatment of mastitis, which is estimated to cost dairy farmers in Britain in excess of £90 million a year, involves widespread use of antibiotics. While farmers are required to observe withdrawal periods, during which milk from cows receiving antibiotic therapy is discarded, the safeguards are not totally effective and some milk may contain significant amounts of antibiotics to which certain consumers are allergic. Other problems arise when bacteria develop antibiotic resistance, allowing pathogenic organisms to spread to the human population. These risks may be exacerbated with bST use, both because it has been shown to increase the incidence of mastitis and because certain bacteria are refractory to antibiotic therapy, as was the case for *Staph. aureus* in the Monsanto study[26].

Public health consequences of changes in consumption of milk and dairy products following product licensing of bST

Milk and dairy products are important components of the diet. For example, in Britain they supply nearly 60% of the calcium and over 20% of protein in the national diet, contribute substantially to needs for vitamins and trace elements[27], and constitute a particularly valuable source of nutrients for young children, adolescents, pregnant and nursing women, the elderly and invalids. While it may not be altogether justified, there is widespread public belief that milk is a 'pure', unadulterated foodstuff.

It is thus important to consider the likely effects on public health of the granting of product licences for bST. In this context, crucially important statistics have been provided by a recent EC survey of public attitudes to biotechnology (the 'Eurobarometer')[28]. Canvassing opinions of 11 800 respondents in the 12 EC countries, the study showed that 79% considered that research on application of biotechnology and genetic engineering to farm animals 'may involve risks to human health or to the environment'. Asked which sources of information were considered to 'tell the truth about biotechnology and genetic engineering', only 1.6% cited 'industry', while 20.1% cited 'school or university' and 32.1% cited 'consumer organizations'. If such opinions are coupled with the fact that much of the research data on bST emanates from the laboratories of the manufacturing companies, and virtually all the rest from laboratories sponsored by those companies (since they are the sole source of recombinant bST), it is not difficult to foresee a major public reaction to the licensing of bST, equivalent to those which have accompanied other recent food scares.

Rejection of milk and dairy products would probably have two types of consequence for public health: decreased intake of valuable nutrients, such as calcium and proteins; and substitution by much less nutritious alternatives.

An example of the likely consequences of the former effect is an increased incidence of osteoporosis. Since milk is the major source of calcium, reduced milk consumption would be likely to exacerbate the already increasing occurrence of this disease. The nature of foods and drinks which might be substituted for milk and dairy products is not easy to discern, since the market might well respond with ostensibly

satisfactory alternatives. However, some indications may be evident in existing trends. For example, between 1982 and 1988 milk consumption by 11-16 year-olds was halved (from 40% to 21% of total drinks consumed), an increased consumption of 'minerals' and fruit juices entirely accounting for the deficit[29]. An increase in the incidence of dental caries is but one likely consequence of this trend.

Conclusions

The assertion that milk from bST-treated cows is safe for consumers is called into question by statements of expert medical committees. Moreover, the analysis of evidence presented by the United States FDA is shown to be less than rigorous.

Certain hazardous effects of bST are known, so that the issues of concern are the extent to which they constitute significant risks. Examples are: adverse changes in the nutrient content of milk, and the increased use of antibiotics which is likely to result from an increased incidence of mastitis.

Other questions are more problematical, such as the extent to which IGF-1 in milk might be biologically active and the food consumption patterns of a public suspicious of new technology. To legalize commercial use of bST in the absence of more extensive information on these questions could lead to a deterioration in public health through widespread rejection of milk, even if increased concentrations of IGF-1 per se are not detrimental. The view has been advanced elsewhere[30] that public confidence in the assessment of biotechnology would be promoted by a more open system of regulation and by the use of 'blind trials' in experimental work.

References

1 Hansen MK. *Biotechnology & milk: benefit or threat?* New York: Consumer Policy Institute, 1990

2 Prosser CG, Mepham TB. Mechanism of action of bovine somatotropin in increasing milk secretion in dairy ruminants. In: Sejrsen K, Neimann-Sorensen A, eds. *Use of somatotropin in livestock production.* London: Elsevier Applied Science, 1989:1-17

3 Bitman J, Wood DK, Tyrrell HF, *et al.* Blood and milk lipid responses induced by growth hormone administration in lactating cows. *J Dairy Sci* 1984;**67**:2873-80

4 Kindstedt PS, Pell AN, Rippe JK, Tsang DS, Hartnell GF. Effect of long-term bovine somatotropin (Sometribove) treatment on nitrogen (Protein) distribution in jersey milk. *J Dairy Sci* 1991;**74**:72-80

5 Eppard PJ, Hudson S, Cole WJ, *et al.* Response of dairy cows to high doses of a sustained-release bovine somatotropin administered during two lactations. 1 Production response. *J Dairy Sci* 1991;**74**:3807-21

6 Juskevich JC, Guyer CG. Bovine growth hormone: food safety evaluation. *Science* 1990;**249**:875-84

7 Baxter RC. The insulin-like growth factors and their binding proteins. *Comp Biochem Physiol* 1988;**91B**: 229-35

8 Prosser CG, Fleet IR, Corps AN. Increased secretion of insulin-like growth factor 1 into milk of cows treated with recombinantly derived bovine growth hormone. *J Dairy Res* 1989;**56**:17-26

9 Honegger A, Humbel RE. Insulin-like growth factors I and II in fetal and adult bovine serum. Purification, primary structures, and immunological cross-reactivities. *J Biol Chem* 1986;**261**:569-75

10 Collier RJ, Miller MA, Hildebrandt JR, *et al.* Factors affecting insulin-like growth factor-1 concentration in bovine milk. *J Dairy Sci* 1991;**74**:2905-2911

11 Corps AN, Brown KD, Rees LH, Carr J, Prosser CG. The insulin-like growth factor 1 content in human milk increases between early and full lactation. *J Clin Endoc Metab* 1988;**67**:25-9

12 Koldovsky O. Search for role of milk-borne biologically active peptides for the suckling. *J Nutr* 1989;**119**: 1546-51

13 American Medical Association, Council on Scientific Affairs. Biotechnology and the American Agricultural Industry. *JAMA* 1991;**265**:1429-36

14 Mesiano S, Young IR, Browne CA, Thorburn GD. Failure of acid-ethanol treatment to prevent interference by binding proteins in radioligand assays for the insulin-like growth factors. *J Endocr* 1988;**119**:453-60

15 Einspanier R, Schams D. Changes in concentrations of insulin-like growth factor, insulin and growth hormone in bovine mammary gland secretion ante and post partum. *J Dairy Res* 1991;**58**:171-8

16 Francis GL, Upton FM, Ballard FJ, McNeil KA, Wallace JC. Insulin-like growth factors 1 and 2 in bovine colostrum. *Biochem J* 1988;**251**:95-103

17 Miller PS, Reis BL, Calvert CC, DePeters EJ, Baldwin RL. Relationship of early lactation and bovine somatotropin on nutrient uptake by cow mammary glands. *J Dairy Sci* 1991;**74**:3800-6

18 Popper KR. *Objective knowledge*, revised edition. Oxford: Oxford University Press, 1979:81

19 Hammond BG, Collier RJ, Miller MA, *et al.* Food safety assessment for the use of BST (bovine somatotropin) in dairy cows. In: *Sometribove: mechanism of action, safety and instructions for use.* [Proceedings of conference held at Telfs, Austria, 1990]. Basingstoke: Monsanto, 1991

20 Schams D. Secretion of somatotropin and IGF-1 into milk during BST administration. In: *Sometribove: mechanism of action, safety and instructions for use.* Basingstoke: Monsanto, 1991

21 Ministry of Agriculture, Fisheries and Food. Medicines Act 1968: *Notes of Applications for Product Licences for Veterinary Medical Products (MAL 10)*: London: MAFF, 1983

22 Malven PV, Head HH, Collier RJ, Buonomo FC. Periparturient changes in secretion and mammary uptake of insulin and in concentrations of insulin and insulin-like growth factors in milk of dairy cows. *J Dairy Sci* 1987;**70**:2254-65

23 Corps AN, Brown KD. Stimulation of intestinal epithelial cell proliferation in culture by growth factors in human and ruminant mammary secretions. *J Endocr* 1987;**113**:285-90

24 National Institutes of Health. Technology assessment conference statement on bovine somatotropin. *JAMA* 1991;**265**:1423-5

25 Kronfeld DS. Biologic and economic risks associated with use of bovine somatotropins. *JAVMA* 1988;**192**:1693-6

26 Cole WJ, Eppard PJ, Boysen BG, *et al.* Response of dairy cows to high doses of a sustained-release bovine somatotropin administered during two lactations. 2. Health and reproduction. *J Dairy Sci* 1992;**75**:111-23

27 Ministry of Agriculture, Fisheries and Food. *Household food consumption and expenditure.* London: HMSO, 1991

28 Commission of European Communities. *Eurobarometer 35.1: Biotechnology.* Brussels: 'CUBE' Biotechnology Unit: 1991

29 National Dairy Council. *Nutrition and teenagers.* London: National Dairy Council, 1989:18

30 Mepham TB. Bovine somatotrophin and public health. *BMJ* 1991;**302**:483-4

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